IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:
Brian Sorrentino et al.

Application No.: 09/866,866 | Confirmation No.: 4688

Filed: May 29, 2001 | Art Unit: 1644

For: ANTIBODIES HAVING BINDING SPECIFICITY FOR THE EXTRACELLULAR DOMAIN OF A BREAST CANCER RESISTANCE PROTEIN (BCRP) (as amended) | Examiner: M. A. Belyavskyi

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPEAL BRIEF

(1) Real Party in Interest

The real party in interest in the present Appeal is St. Jude Children's Research Hospital, the assignee, as evidenced by the assignment set forth at Reel 012121 Frame 0660.

(2) Related Appeals and Interferences

None.

(3) Status of Claims

This application contains claims 16, 22-24, and 29-34, each of which were finally rejected in an Office Action mailed May 14, 2007. On August 14, 2007 Appellant appealed from the final rejection of claims 16, 22-24, and 29-34 (all claims currently under examination in this application).

(4) Status of Amendments

No amendments have been made since the Office Action mailed May 14, 2007.

(5) Summary of Claimed Subject Matter

One aspect of Appellant's invention, as recited in independent claim 16, provides an isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) (specification, page 8, lines 16-25; page 15, lines 1-16); wherein the extracellular portion of the BCRP is in its natural conformation (specification, page 9, lines 22-23); wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface (specification, page 39, line 5 - page 40, line 2); wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface (specification, page 23, lines 25-29; page 39, lines 19-22; page 22, line 26 -page 24, line 17); and wherein the antibody does not bind to denatured BCRP (specification, page 23, lines 13-26; page 22, line 26 - page 24, line 17).

Another aspect of Appellant's invention, as recited in independent claim 31, is an antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) (specification, page 8, lines 16-25; page 15, lines 1-16) generated by three steps. These three steps are (i) immunizing an animal with 3T3 cells that express huBCRP or mBCRP in its natural conformation on the cell surface (specification, page 9, lines 22-23; page 39, line 5 - page 40, line 2); (ii) selecting a hybridoma that secrets antibodies that bind to MCF-7 cells that express huBCRP or mBCRP in its natural conformation on the cell surface, said antibodies do not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface, and do not bind to denatured BCRP (specification, page 23, lines 13-29; page 39, lines 19-22; page 22, line 26 - page 24, line 17); and (iii) isolating an antibody from the hybridoma selected in step (ii) (specification, page 39, line 30 - page 40, line 2).

In yet another aspect of Appellant's invention, as recited in independent claim 33, an isolated antibody is claimed. The antibody claimed in claim 33 binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) (specification, page 8, lines 16-25; page 15, lines 1-16; page 9, lines 22-23) generated by isolating an antibody from a hybridoma that secretes

antibodies that bind to MCF-7 cells (specification, page 39, line 17 - page 40, line 2) that express buBCRP or mBCRP in its natural conformation on the cell surface (specification, page 23, lines 25-29; page 39, lines 19-22), wherein said antibodies do not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface (specification, page 23, lines 25-29; page 39, lines 19-22); wherein said antibodies do not bind to denatured BCRP (specification, page 23, lines 13-16; page 22, line 26 - page 24, line 17); and wherein the hybridoma is generated from an animal immunized with 3T3 cells that express huBCRP or mBCRP in its natural conformation on the cell surface (specification, page 39, line 13 - page 40, line 2).

(6) Grounds of Rejection to be Reviewed on Appeal

The following grounds for rejection will be reviewed on this appeal:

I. claims 16, 22-24, and 29-34 were rejected under 35 U.S.C. § 112, second paragraph as indefinite;

II. claims 16, 22-24, and 29-34 were rejected under 35 U.S.C. § 112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." *See* Office Action mailed May 14, 2007 at 3;

III. claims 16, 22, and 31-34 were rejected under 35 U.S.C. § 102(e) in view of U.S. Patent No. 6,313,277 ("the '277 patent");

IV. claims 16, 22-24, and 29-34 were rejected under 35 U.S.C. § 102(e) in view of U.S. Patent No. 6,485,933 ("the '933 patent");

V. claims 16, 23, 24, and 29 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '277 patent in view of Owens *et al.*, *J. of Immunological Methods 168*: 149-165 (1994) ("Owens"); and

VI. claims 16 and 30 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '277 patent or the '933 patent each in view of U.S. Patent No. 4,281,061 ("the '061 patent") in view of Owens.

(7) Argument

Summary of the Invention

The subject application is directed, generally, to isolated antibodies that bind to an extracellular portion of a Breast Cancer Resistance Protein (BCRP). Applicant discovered that BCRP is uniquely expressed on the surface of hematopoietic stem cells and, accordingly, that antibodies that bind to the extracellular domain of the BCRP protein in its natural conformation may be utilized for the detection and isolation of hematopoietic stem cells. Applicant also recognized, and disclosed in their specification, that antibodies that bind to the intracellular regions of BCRP and/or to denatured BCRP would be ineffective in isolating viable hematopoietic stem cells.

Applicant exemplified the preparation of antibodies that are specific for the extracellular domain of BCRP in its natural conformation by describing: (1) the use of 3T3 cells expressing BCRP to immunize mice, and (2) the use of the human breast cancer cell line MCF-7 made to express BCRP in screening assays for identifying antibodies that bind to the BCRP extracellular domain in its natural conformation. Applicant further confirmed that antibodies that bind to BCRP in its natural conformation on MCF-7 cells are unable to bind to parental MCF-7 cells that do not express BCRP.

Because the resulting antibodies are raised against the extracellular domain of BCRP in its natural conformation, Applicant specifically excluded antibodies that bind to denatured BCRP. And, the skilled artisan, fully apprised of the teachings of Applicant's specification, would readily recognize that antibodies that bind to the intracellular domain of BCRP or to denatured BCRP would be ineffective in detecting and isolating viable hematopoietic stem cells that express BCRP in its natural conformation.

Accordingly, Applicant's presently claimed invention is directed to isolated antibodies that bind to an extracellular portion of a human or a murine BCRP, wherein the extracellular portion of BCRP is in its natural conformation, and wherein the antibody binds to living MCF-7 or 3T3 cells that express BCRP on their surface. Moreover, Applicant's claims specifically exclude antibodies that bind to living MCF-7 cells that do not express BCRP and antibodies that bind to denatured BCRP. Thus, in contrast to antibodies generated against purified and/or denatured BCRP, the antibodies covered by Applicant's claimed invention will, for example, find utility in the isolation of viable hematopoietic stem cells and other cells that express BCRP in its natural conformation.

I. Patentability of Claims 16, 22-24, and 29-34 Under 35 U.S.C. § 112, ¶ 2.

a. Read in light of the specification, claims 16, 22-24, and 29-34 are sufficiently definite.

Applicant respectfully submits that the Examiner erred in rejecting claims 16, 22-24, and 29-34 as indefinite under 35 U.S.C. § 112, ¶ 2. The rejected claims specify either huBCRP or mBCRP. The terms "huBCRP" and "mBCRP" are not indefinite because, reading the specification, one of ordinary skill in the art knows that these terms correspond to a set of well-defined proteins, identified by SEQ ID in the specification. There is no ambiguity in what is claimed by using the terms huBCRP and mBCRP.

Reciting SEQ ID numbers for BCRP in the claims is *not* required where, as here, the specification defines BCRP on a species-specific basis and recites SEQ IDs for a given species. Where the claim terms can be read in light of the specification to provide notice to one of ordinary skill in the art of the scope of the invention, those claims are not indefinite under § 112, ¶ 2. *See All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779-80, 64 USPQ2d 1945 (Fed. Cir. 2002). "The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, *e.g.*, competitors of the patent owner, can determine whether or not they infringe." *Id.* (citation omitted). In this case, the claim terms "huBCRP" and "mBCRP" are species-specific proteins defined in the specification according to their respective SEQ ID numbers.

The term "BCRP" as used and defined in the specification (page 3, lines 28-31) refers to a genus of proteins from individual mammalian species. SEQ ID numbers are provided for individual species-specific BCRP sequences in the specification as filed, for example at page 8, lines 16-21, and at page 15, lines 10-16. Also, "BCRP" is defined on page 15, lines 6-7 as including "all of such ATP transport proteins obtained from any mammalian source." For example, the specification at ¶ 0051, specifically states that:

> One huBCRP gene product which is encoded by the nucleotide sequence of SEQ ID NO: 9 and has the amino acid sequence of SEQ ID NO: 10, whereas another variant is encoded by the nucleotide sequence of SEQ ID NO: 26 and has the amino acid sequence of SEQ ID NO: 27. One mBCRP is encoded by the nucleotide sequence of SEQ ID NO: 13 and has the amino acid sequence of SEQ ID NO: 14 and another mBCRP is encoded by a nucleotide sequence comprising SEQ ID NO: 11 and has an amino acid sequence comprising SEQ ID NO: 12.

In the pending claims, "BCRP" is used to denote the genus of Breast Cancer Resistance Proteins, while "human or murine BCRP" is used to denote the species-specific Breast Cancer Resistance Protein, huBCRP or mBCRP. The instant claims specifically include references to "human BCRP" or "huBCRP" and "murine BCRP" or "mBCRP," where appropriate, to refer to species-specific BCRPs and their respective SEQ IDs as set forth in the specification.

In view of the teaching in the specification clearly and distinctly describing species-specific BCRP with reference to SEQ ID, there is no need to include those SEQ ID numbers in the claims.

II. Patentability of Claims 16, 22-24, and 29-34 Under 35 U.S.C. § 112, ¶ 1.

Applicant respectfully submits that the Examiner erred in rejecting these claims under 35 U.S.C. § 112, ¶ 1. The Examiner states that these claims are rejected under § 112, ¶ 1 for "the same reasons set forth in the previous Office Action, mailed 11/07/06. **This is a New Matter Rejection.**" Office Action mailed May 14, 2007 at 3, ¶ 6 (emphasis in the original). The Examiner concedes that the specification and claims as originally filed support an "antibody that recognized an extracellular portion of BCRP, wherein said extracellular portion of the BCRP is in its natural conformation" but alleges that the claim language:

> wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface; wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface; and wherein the antibody does not bind to denatured BCRP (Claim 16)

"represent(s) a departure from the specification and the claims as originally filed and applicant has not pointed out where the support come(s) from." Office Action mailed November 7, 2006 at 3, ¶ 7.

Support for the language in amended claim 16 may be found throughout the application as filed such as, for example, at page 39, line 5 thru page 40, line 2, which describes: (1) the generation of hybridomas from mice immunized with 3T3-BCRP cells, (2) screening of the hybridomas with MCF-7 cells, both transduced with an amphotrophic HaBCRP vector (screen) and untransduced (back-screen), and (3) production of BCRP-specific antibodies. Further support for the recited claim language may be found at page 22, line 26 thru page 24, line 17, which describes (1) methods for producing BCRP antibodies involving use of 3T3 and MCF-7 cells and (2) the use of transduced living cells to increase the probability of detection by the immune system of external huBCRP epitopes in their native conformation rather than internal epitopes or denatured epitopes. Support is also found at page 23, lines 13-16 where the following is stated: "[t]he strategy of using living cells transduced with the vector increases the probability that the immune system will detect external huBCRP epitopes in their native configuration, rather than epitopes that are internally located in the cells, or epitopes only present in denatured protein."

Because the specification as filed contained the above description of antibodies that bind to an extracellular portion of a human or mouse BCRP, which antibodies bind to the extracellular portion of BCRP in its natural conformation and to living MCF-7 or 3T3 cells expressing BCRP on their surface and which antibodies do not bind to living MCF-7 cells that do not express BCRP on their surface and do not bind to denatured BCRP, no "new matter" was added by Applicant's amendments to claim 16 and there can be no dispute that the specification demonstrates that Applicant was in possession of what was claimed at the time the application

was filed. *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345-46, 54 USPQ2d 1915 (Fed. Cir. 2000).

III. The Rejection of Claims 16, 22, and 31-34 Under 35 U.S.C. § 102(e) in view of the '277 Patent.

Applicant respectfully submits that the Examiner erred in rejecting claims 16, 22 and 31-34 under 35 U.S.C. § 102(e) in view of the '277 patent. The Examiner alleges that the '277 patent teaches polyclonal and monoclonal antibodies that bind to a BCRP. While the Examiner concedes that the '277 patent does not expressly disclose antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP, the Examiner alleges that such functional limitations are inherent properties of the antibodies taught by the '277 patent "because the referenced antibody was obtained against the same antigen as claimed." Office Action mailed May 14, 2007 at 4. The Examiner further alleges that Applicant bears the burden of proving a lack of inherent properties in the cited art given the lack of laboratory facilities at the USPTO. *Id.* (citing *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-93 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 2005 USPQ 594 (CCPA 1980)).

Applicant respectfully submits that the Examiner is wrong in rejecting claims 16, 22 and 31-34 under 35 U.S.C. § 102(e) in view of the '277 patent. The elements of those claims are *not* disclosed in the '277 patent under a theory of inherency. Moreover, the Examiner bears the burden of proving anticipation under a theory of inherency by providing a rationale or evidence that supports inherent anticipation, as set forth in the MPEP at § 2112, ¶ IV. This is not a matter of having adequate laboratory facilities, but one involving a complete lack of technical reasoning or evidence showing that the claimed features are inherently present in the prior art.

a. Legal framework for anticipation by inherency.

The Examiner bears the burden of "provid[ing] rationale or evidence tending to show inherency." As stated in the MPEP,

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

MPEP § 2112 ¶ IV (quoting *Ex parte Levy,* 17 USPQ2d 1461, 1464 (B.P.A.I. 1990) (reversing the Examiner on the basis that the Examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency)) (emphasis added and in the original).

To anticipate under a theory of inherency, the prior art must "necessarily function[] in accordance with, or include[], the claimed limitations . . . ." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943 (Fed. Cir. 1999) (emphasis added). Results must be the necessary consequence of what is deliberately intended. *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 52 USPQ2d 1303 (Fed. Cir. 1999) (emphasis added). "A limitation or the entire invention is inherent and in the public domain only if it is the 'natural result flowing from' the explicit disclosure of the prior art." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377, 77 USPQ2d 1321 (Fed. Cir. 2005) (quoting *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379, 67 USPQ2d 1664 (Fed. Cir. 2003)) (emphasis added).

Occasional results are not, however, inherent. *MEHL/Biophile*, 192 F.3d at 1365. "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112 (quoting *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) (reversing rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art)) (citing *In re Oelrich*, 666 F.2d 578 (CCPA 1981)) (emphasis added).

"An invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species).

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would

be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" MPEP § 2112 ¶ IV (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)) (emphasis added) (citations omitted). There can be no anticipation where the record does not show conclusively that the prior art produced the claimed subject matter. *Schering*, 339 F.3d at 1378.

b. The '277 patent does not disclose antibodies that bind to an extracellular portion of BCRP and that do not bind to denatured BCRP.

Contrary to the Examiner's assertions, the burden is on the PTO to prove invalidity by inherency. MPEP § 2112 ¶ IV. Thus, the PTO must show, either "by rationale or evidence," that the '277 patent necessarily discloses antibodies that "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[] not bind to denatured BCRP" as recited in the instant claims. By failing to present any rationale or evidence supporting a theory of inherent anticipation, the Examiner has failed to meet the burden of establishing a *prima facie* case for inherent anticipation.

The '277 patent discloses that "[a] polyclonal antibody capable of binding to BCRP can be prepared by immunizing a mammal with a preparation of BCRP or functional derivative of BCRP." (Col. 4, lines 50-52; emphasis added). The '277 patent also discloses that "[monoclonal] antibodies can be produced by immunizing splenocytes with activated BCRP." (Col. 4, lines 54-57; emphasis added; citation omitted). Thus, the '277 patent does not, in fact, disclose the *actual generation* of any antibody, let alone one that would necessarily bind to an extracellular portion of BCRP and ***not*** to denatured BCRP. This omission in the '277 patent is significant because there is nothing within the '277 patent from which one skilled in the art could deduce to what portion (if any) of BCRP the disclosed antibody would bind. Thus, the '277 patent does not "make clear that the missing descriptive matter is necessarily present in the thing described in the reference." MPEP § 2112 ¶ IV (emphasis added). The '277 patent offers no clue regarding the highly variable functional attributes possessed by antibodies binding to BCRP. On the contrary, the claims at issue in this case are defined by specific functional attributes, none

of which are discussed or even suggested in the '277 patent. Further, the Examiner offers no rational basis for concluding that these functional attributes are "necessarily present" in the antibodies disclosed in the '277 patent.

Applicant does not claim any antibody that binds to BCRP. Applicant specifically claims antibodies that, *inter alia*, bind to an extracellular portion of a BCRP and do not bind to a denatured BCRP. The mere possibility that an antibody generated by the methods suggested in the '277 patent might bind to "an extracellular portion of a BCRP" and/or might not bind "to denatured BCRP" is not sufficient to establish that antibodies generated by the methods disclosed in the '277 patent would necessarily possess those activities. Thus, the '277 patent cannot be said to inherently disclose the antibodies of instant claims 16 and 22.

Indeed, as pointed out by Dr. Sarkadi in his Declaration (filed Oct. 28, 2003), the '277 patent teaches antibodies prepared against a *purified* protein, not against a BCRP in its natural conformation. This is critical because BCRP adopts a "very different" conformation upon purification as compared to its natural conformation within the context of a cell membrane. Also, as Dr. Sarkadi emphasized, "with respect to the extracellular domain of BCRP, it is important to note that BCRP forms a homodimer. The BCRP homodimer would be expected to adopt a very different conformation than the monomeric purified protein or purified protein fragment. As a result, any antibody generated against a purified BCRP protein, or fragment of a BCRP protein would not be expected to recognize the extracellular domain of the BCRP protein in its natural conformation embedded in the cell membrane." (Sarkadi Declaration ¶5). It is clear that antibodies raised against a purified protein, as disclosed in the '277 patent, would not necessarily bind to and, in fact, would most probably not bind to, the extracellular portion of a BCRP. Thus, the '277 patent cannot be said to inherently disclose antibodies according to the presently claimed invention.

Furthermore, as Dr. Sarkadi explained in the Supplemental Declaration (filed Feb. 22, 2005), "[a]s antibodies can recognize conformational epitopes, the three-dimensional structure is critical for production and recognition of an epitope composed of a specific domain (*e.g.*, extracellular portion) in a particular conformation (*e.g.*, the natural conformation)." (Sarkadi

Supplemental Declaration ¶5). In support of his Supplemental Declaration, Dr. Sarkadi discussed his 2004 publication (Ozvegy-Laczka *et al.*, submitted with the Supplemental Declaration) wherein it was demonstrated that the binding of antibody 5D3 to an extracellular epitope of BCRP in its natural conformation "is dependent upon the actual conformation within the transport cycle of this multidrug resistance protein. In contrast, an antibody generated against an N-terminal intracellular epitope of BCRP (*i.e.* BXP-21) cannot recognize BCRP in a living cell." (Sarkadi Supplemental Declaration ¶7). Thus, Dr. Sarkadi concludes that "this method is essential to producing an antibody which recognizes an extracellular portion of BCRP in its natural conformation." *Id.*

Because the '277 patent does not disclose, either expressly or inherently, antibodies or methods for preparing antibodies that necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[] not bind to denatured BCRP," the '277 patent does not anticipate any of the instant claims.

c. With respect to claims 31-34, the '277 patent does not disclose the claimed antibody.

As explained above with respect to claims 16 and 22, the '277 patent does not inherently disclose an antibody or methods for preparing antibodies that necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[] not bind to denatured BCRP." Because claims 31-34 claim an antibody having these functional properties, they are not anticipated by the '277 patent for the same reasons set forth above with respect to claims 16 and 22.

The Examiner alleges that, since claims 31-34 are directed to a product, the patentability of the product does not depend on its method of production. Office Action of May 14, 2007 at 4 (citing *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985); MPEP § 2113)). The Examiner further cites *Noelle v. Lederman*, 355 F.3d 1343, 69 USPQ2d 1508 (Fed. Cir. 2004), arguing that the '277 patent "disclosed a fully characterized BCRP antigen by its structure." *Id.* at 5. Both cases are inapplicable in the present situation because the Examiner has failed to meet his burden of establishing a *prima facie* case of unpatentablity of the product claimed in claims 31-34.

Thorpe, 777 F.2d 695, 697 ("The burden of presenting a *prima facie* case of unpatentability resides with the PTO . . . ."). The product claimed in claims 31-34 is not just *any* antibody, but one that "binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[es] not bind to denatured BCRP." The Examiner has not shown the existence of this product in the prior art and has not provided any rationale why this product would be inherent in the cited art. Thus, claims 31-34 are not anticipated by the art cited by the Examiner.

IV. The Rejection of Claims 16, 22-24, and 29-34 Under § 102(e) in view of the '933 Patent.

a. The '933 patent does disclose antibodies that bind to an extracellular portion of BCRP and that do not bind to denatured BCRP.

The Examiner's rejection of claims 16, 22-24, and 29-34 under § 102(e) in view of the '933 patent is flawed for many of the same reasons stated above with respect to the '277 patent. In short, much like the '277 patent, the '933 patent also fails to disclose an antibody or methods for preparing antibodies that necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[] not bind to denatured BCRP." These elements establish novelty of claims 16, 22-24, and 29-34 under § 102 over the '933 patent.

The Examiner alleges that the '933 patent teaches a polyclonal and monoclonal antibody that binds to BCRP. Office Action of May 14, 2007 at 5. While the Examiner concedes that the '933 patent does not expressly disclose antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP, the Examiner alleges that such functional limitations are inherent properties of the antibodies taught by the '933 patent "because the referenced antibody was obtained against the same antigen as claimed." *Id.* The Examiner further alleges that the burden is on Applicant to prove otherwise given the lack of laboratory facilities at the USPTO. *Id.* (citing *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-93 (Fed. Cir. 1983); *In re Fitzgerald*, 2005 USPQ 594 (CCPA 1980)). For many of the same reasons already stated above with respect to the '277 patent, the Examiner's arguments are flawed.

The '933 patent discloses that "[a] variety of protocols for detecting and measuring the expression of BCRP, using either polyclonal or monoclonal antibodies specific for the protein are known in the art." (Col. 16, lines 16-18; emphasis added). Thus, the '933 patent does not, in fact, disclose any antibody. Rather, the '933 patent discloses assay systems such as "enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS)" that could be employed to detect the expression of BCRP "using either a polyclonal or monoclonal antibod[y]." Appellant submits that such prophetic disclosure of purely hypothetical antibodies does not support the Examiner's assertion that antibodies disclosed in the '933 patent would necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "not bind to denatured BCRP" as recited in the instant claims. There is nothing within the '933 patent from which one skilled in the art could deduce to what, if any, portion of BCRP an antibody disclosed in the '933 patent would bind. Thus, the '933 patent does not "make clear that the missing descriptive matter is necessarily present in the thing described in the reference."

Appellant once again refers to the Sarkadi Declaration where it is explained that antibodies raised against a purified protein, as disclosed in the '933 patent, would not necessarily bind to and, in fact, *would most probably not bind to*, the extracellular portion of a BCRP. And contrary to the Examiner's assertions, the burden is on the PTO to prove invalidity by inherency. MPEP § 2112 ¶ IV. Thus, the PTO must show that the '933 patent necessarily discloses antibodies that "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[] not bind to denatured BCRP" as recited in the instant claims. The Examiner has failed to meet this burden.

b. With respect to dependent claims 23, 24, and 29, the '933 patent does not expressly or inherently disclose antibodies that are chimeric, humanized, or attached to a detectable label.

Because claims 23, 24, and 29 depend from claim 16, they are patentably distinct from the '933 patent on the grounds asserted above with respect to claim 16. By including further elements describing antibodies that are chimeric, humanized, or attached to a detectable label, claims 23, 24, and 29 are further distinct from the '933 patent. The '933 patent fails to disclose

an antibody or methods for preparing antibodies that "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[] not bind to denatured BCRP" where those antibodies are also "chimeric" (claim 23), "humanized" (claim 24), or "attached to a detectable label" (claim 29). For these additional reasons, claims 23, 24, and 29 are patentably distinct from the '933 patent.

c. With respect to claims 31-34, the '933 patent does not disclose the claimed antibody.

As explained above with respect to claims 16, 22-24 and 29-34, the '933 patent does not inherently disclose an antibody or methods for preparing antibodies that necessarily "bind[] to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[] not bind to denatured BCRP." Because claims 31-34 claim an antibody having these functional properties, they are not anticipated by the '933 patent for the same reasons set forth above with respect to claims 16 and 22-24.

The Examiner alleges that, since claims 31-34 are directed to a product, the patentability of the product does not depend on its method of production. Office Action of May 14, 2007 at 5-6 (citing *Thorpe*, 227 USPQ at 966; MPEP § 2113)). The Examiner further cites *Noelle v. Lederman*, 355 F.3d 1343, 69 USPQ2d 1508 (Fed. Cir. 2004) arguing that the '933 patent "disclosed a fully characterized BCRP antigen by its structure." *Id.* at 4-5. Both cases are inapplicable in the present situation because the Examiner has failed to meet his burden of establishing a *prima facie* case of unpatentablity of the product claimed in claims 31-34. *Thorpe*, 777 F.2d at 697 ("The burden of presenting a *prima facie* case of unpatentability resides with the PTO . . . ."). The product claimed in claims 31-34 is not just *any* antibody, but one that "binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP)" and/or "do[es] not bind to denatured BCRP." The Examiner has not shown the existence of this product in the prior art and has not provided any rationale why this product would be inherent in the cited art. Thus, claims 31-34 must be patentable over the cited references.

V. The Rejection of Claims 16, 23, 24, and 29 Under § 103(a) as Allegedly Obvious over the '277Ppatent in view of Owens.

a. Legal framework for obviousness.

In this case, the Examiner has failed to set forth a *prima facie* case for obviousness for claims 16, 23, 24, and 29. Under *Graham v. John Deere Co.*, 383 U.S. 1 (1965), there are several basic factual inquiries that must be considered under 35 U.S.C. §103 in evaluating the obviousness of an invention:

1. The scope and content of the prior art;
2. Differences between the prior art and the claims at issue; and
3. The level of ordinary skill in the pertinent art.

Graham, 383 U.S. at 17.

With respect to the first two of these factors, MPEP § 2143.03 makes clear that: "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). 'All words in a claim must be considered in judging the patentability of that claim against the prior art.' *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)."

Although the recent Supreme Court decision in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) has relaxed the test for combining references, it made no change in the *Graham* factors or in the requirements noted above that all claim limitations must be taught or suggested by the prior art. The Supreme Court noted with approval *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006), which stated that "[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

b. A prima facie case of obviousness cannot be made because the elements of claims 16, 23, 24, and 29 cannot be found in the '277 patent in view of Owens.

Claims 16, 23, 24, and 29 stand rejected as allegedly obvious over the '277 patent in view of Owens *et al.*, *J. of Immunological Methods 168*:149-165 (1994) (hereinafter, "Owens"). The combination of the '277 patent and Owens, viewed as a whole, neither teaches nor suggests the

subject matter of claims 16, 23-24, and 29. As addressed in connection with the Examiner's rejection under § 102(e) and as conceded by the Examiner, the '277 patent "is silent" with respect to antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP. Office Action mailed May 14, 2007 at 4. Because Owens does not, *inter alia*, remedy these deficiencies in the '277 patent, none of claims 16, 23-24, and 29 can be obvious over the '277 patent in view of Owens.

On the contrary, Owens' teachings with respect to antibodies are extremely generalized with respect to *any antibody* and fail to provide any guidance to the skilled artisan otherwise motivated to generate an antibody to BCRP. Assuming, *arguendo*, that the Examiner is correct in alleging that "it would have been prima facie obvious . . . to produce the monoclonal antibody taught by US Patent '277 as chimeric, humanized antibody, taught by the Owens *et al*," such a teaching would not have led the skilled artisan to Applicant's claimed invention because neither reference teaches or suggests an antibody that (1) binds to an extracellular portion of a BCRP and (2) does not bind to a denatured BCRP.

The Examiner's allegations fail to appreciate the distinction between antibodies suggested in the '277 patent that are proposed to be generated against a purified BCRP versus antibodies that bind to an extracellular portion of a BCRP but not to a denatured BCRP. As discussed above in reference to Dr. Sarkadi's Declaration, "any antibody generated against a purified BCRP protein, or fragment of a BCRP protein would not be expected to recognize the extracellular domain of the BCRP protein in its natural conformation embedded in the cell membrane." (Sarkadi Declaration ¶5).

Because the '277 patent fails to teach or suggest antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP, and because Owens fails to remedy this deficiency, Appellant respectfully submits that each of claims 16, 23-24, and 29 are nonobvious over the '277 patent in view of Owens when these references are viewed for the whole of their teachings.

With respect to claims 23, 24, and 29, the Examiner concedes that the '277 patent does not teach an isolated antibody wherein the antibody is chimeric (as recited in claim 23) or humanized (as recited in claim 24) or attached to a detectable label (as recited in claim 29). Office Action mailed May 14, 2007 at 7. The Examiner alleges, however, that Owens remedies these deficiencies by teaching modification of murine antibodies such as chimeric antibodies, single chain antibodies, humanized antibodies, or attaching a detectable label to an antibody. *Id.* Thus, the Examiner alleges that it would have been obvious to a person having skill in the art to combine the teachings of the '277 patent and of Owens to achieve Applicant's invention and that the person of skill in the art would have been motivated to make such a combination because of the various advantages of each antibody type over unmodified antibodies, and that they would have had a reasonable expectation of success in doing so. Because, however, Owens does not remedy any of the deficiencies noted in the '277 patent, claims 23, 24, and 29 cannot be obvious over the combination of the '277 patent and Owens.

VI. The Rejection of Claims 16 and 30 Under § 103(a) as Allegedly Obvious over the '277 patent or the '933 patent each in view of the '061 Patent in view of Owens

a. A prima facie case of obviousness cannot be made because the elements of claims 16 and 30 cannot be found in the '277 patent, the '933 patent, the '061 patent, or in Owens.

Claims 16 and 30 stand rejected as allegedly obvious over either the '277 patent or the '933 patent in view of U.S. Patent No. 4,281,061 (the '061 patent) in view of Owens. As addressed above in connection with the Examiner's rejection under § 102(e), and as conceded by the Examiner, the '277 patent and the '933 patent "are silent" with respect to antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP. Office Action mailed May 14, 2007 at 4, 5. Because neither the '061 patent nor Owens remedies these deficiencies in the '277 and '933 patents, neither claim 16 nor claim 30 can be obvious over the '277 patent or '933 patent in view of the '061 patent or Owens. On the contrary, the '061 patent's teachings with respect to "pharmaceutical compositions provided as kits" are extremely generalized with respect to *any double antibodies* for enhanced sensitivity in immunoassays, and

fail to provide any guidance to the skilled artisan otherwise motivated to generate a kit comprising an antibody to BCRP.

Assuming *arguendo* that the Examiner is correct in alleging that "[o]ne of ordinary skill in the art at the time of the invention was made . . . [would have been motivated to assemble] the reagents in a kit format" as allegedly taught by the '061 patent, such a teaching would not have led the skilled artisan to Applicant's claimed invention because the '061 reference neither teaches nor suggests an antibody that (1) binds to an extracellular portion of a BCRP and (2) does not bind to a denatured BCRP.

The Examiner's allegations fail to appreciate the distinction between antibodies suggested in the '277 and '933 patents that are proposed to be generated against a purified BCRP versus antibodies that bind to an extracellular portion of a BCRP but not to a denatured BCRP. As discussed above in reference to Dr. Sarkadi's Declaration, "any antibody generated against a purified BCRP protein, or fragment of a BCRP protein would not be expected to recognize the extracellular domain of the BCRP protein in its natural conformation embedded in the cell membrane." (Sarkadi Declaration ¶5).

Because the '277 patent and the '933 patent both fail to teach or suggest antibodies that (1) bind to an extracellular portion of a BCRP and (2) do not bind to a denatured BCRP and because the '061 patent and Owens fail to remedy this deficiency, Appellant respectfully submits that each of claims 16 and 30 are nonobvious over the '277 patent or the '933 patent in view of the '061 patent when these references are viewed for the whole of their teachings.

With respect to claim 30, the Examiner concedes that neither the '277 patent nor the '933 patent teaches a kit. Office Action Mailed May 14, 2007 at 8. The Examiner alleges, however, that the '061 patent remedies that deficiency by teaching that reagents of pharmaceutical compositions can be provided as kits. *Id.* Thus, the Examiner alleges that it would have been obvious to combine the teachings of either of the '277 or '933 patents with the kit of the '061 patent to achieve Applicants' claimed invention. *Id.* The combination of either the '277 patent or

the '933 patent in view of the '061 patent or Owens neither teaches nor suggests the subject matter recited in claim 30.

Dated: November 14, 2007

Respectfully submitted,

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APPENDIX A

Claims under appeal:

16. An isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP); wherein the extracellular portion of the BCRP is in its natural conformation; wherein the antibody binds to living MCF-7 or 3T3 cells expressing BCRP on their surface; wherein the antibody does not bind to living MCF-7 cells that do not express BCRP on their surface; and wherein the antibody does not bind to denatured BCRP.

22. The isolated antibody of claim 16 wherein the isolated antibody is monoclonal.

23. The isolated antibody of claim 16 wherein the isolated antibody is chimeric.

24. The isolated antibody of claim 23 wherein the antibody is humanized.

29. The isolated antibody of claim 16, operably attached to a detectable label.

30. An immunodetection kit comprising, in suitable container means, the antibody according to claim 16 and an immunodetection reagent.

31. An isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) generated by

(i) immunizing an animal with 3T3 cells that express huBCRP or mBCRP in its natural conformation on the cell surface;

(ii) selecting a hybridoma that secretes antibodies that bind to MCF-7 cells that express huBCRP or mBCRP in its natural conformation on the cell surface, said antibodies do

not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface, and do not bind to denatured BCRP; and

(iii) isolating an antibody from the hybridoma selected in step (ii).

32. The antibody of claim 31, which is generated in a mouse and wherein the BCRP is human BCRP.

33. An isolated antibody that binds to an extracellular portion of a Breast Cancer Resistance Protein (BCRP) selected from the group consisting of human BCRP (huBCRP) or murine BCRP (mBCRP) generated by isolating an antibody from a hybridoma that secretes antibodies that bind to MCF-7 cells that express huBCRP or mBCRP in its natural conformation on the cell surface, said antibodies do not bind to MCF-7 cells that do not express huBCRP or mBCRP in its natural conformation on the cell surface, and said antibodies do not bind to denatured BCRP, and wherein the hybridoma is generated from an animal immunized with 3T3 cells that express huBCRP or mBCRP in its natural conformation on the cell surface.

34. The antibody of claim 33, wherein the animal is a mouse and the BCRP is human BCRP.

APPENDIX B – EVIDENCE

Sarkadi Declaration - OIPE date stamped October 28, 2003

Sarkadi Supplemental Declaration - OIPE date stamped February 22, 2005

OIPE
OCT 2 8 2003
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	SJ-0015
Inventors:	Sorrentino and Schuetz
Serial No.:	09/866,866
Filing Date:	May 29, 2001
Examiner:	Li, Qian J.
Group Art Unit:	1632
Title:	Method of Identifying and/or Isolating Stem Cells and Prognosing Responsiveness to Leukemia Treatment

DECLARATION

1. I, Dr. Balazs Sarkadi, M.D., Ph.D. am a medical doctor affiliated with National Medical Center in Budapest, Hungary. Based upon my qualifications as set forth in the attached curriculum vitae and list of publications, I am an expert in the field of ABC transporters, especially as it pertains to the generation of antibodies to ABC transport proteins including BCRP.

2. I have reviewed the Office action issued in this case dated May 21, 2003. I have further reviewed and understand the prior art methods taught by Ross (U.S. Patent 6,313,277) and

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Niman (U.S. Patent 5,563,247) as identified by the Examiner in the Office action.

3. As of the priority date of May 31, 2000 there was no method known in the art to reliably produce an isolated antibody that recognizes an extracellular portion of the ABC transporter BCRP(ABCG2) in a living cell. One of skill in this field would not have expected that conventional methods available for generating antibodies as of May 31, 2000 could be used to generate an antibody that would specifically recognize the extracellular portion of BCRP on a cell.

4. In particular, someone skilled in the field of antibody production would not have reasonably expected to be able to produce an antibody that recognizes the extracellular portion of BCRP in its natural conformation, using the prior art methods taught by Ross (U.S. Patent 6,313,277) and Niman (U.S. Patent 5,563,247), as suggested by the Examiner.

5. Ross teaches antibodies prepared against a purified protein. A purified protein can have a very different conformation than the conformation that exists when the protein is in its natural state (i.e. natural conformation). ABC transporter proteins, particularly including BCRP, adopt a very

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different conformation when they are purified compared to their natural conformation imbedded in the cell membrane. With respect to the extracellular domain of BCRP, it is important to note that BCRP forms a homodimer. The BCRP homodimer would be expected to adopt a very different conformation than the monomeric purified protein or purified protein fragment. As a result, any antibody generated against a purified BCRP protein, or fragment of a BCRP protein would not be expected to recognize the extracellular domain of the BCRP protein in its natural conformation embedded in the cell membrane.

6. The Niman reference discloses a method of making an antibody to a cell surface protein by using a whole cell technique. This general technique of using whole cells as immunogens to generate antibodies to extracellular epitopes of cell membrane proteins does not work well for ABC transporters. ABC transporters, particularly those such as BCRP, are only weakly expressed and have only a few small extracellular domains which are poor targets for antibodies. Therefore, the

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method for generating antibodies disclosed in Niman would not be expected to successfully generate antibodies to the extracellular domain of BCRP.

I hereby declare that all statements herein of our own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or by imprisonment, or both under §1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application, any patent issuing there upon, or any patent to which this verified statement is directed.

Dr. Balazs Sarkadi, M.D., Ph.D.

Date: Octobe 27/2003

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CURRICULUM VITAE

Name: Balázs Sarkadi, M.D., Ph.D., D.Sc.
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(phone: 36-1-395-1816)
Office: National Medical Center, Institute of Haematology and Immunology, Diószegi u. 64, 1113 Budapest, Hungary , (phone/fax: 36-1-372-4353)
Date and place of birth: May 30, 1948, Budapest, Hungary
Citizenship: Hungarian
Family status: Married, two children (born in 1974 and 1979)
Education:
- Semmelweis University Medical School, Budapest, Hungary, 1966-1972;
- M.D. degree: Budapest, 1972;
- Ph.D. degree: Hungarian Academy of Sciences, 1980;
- Doctor of Biological Sciences: Hungarian Academy of Sciences, 1986

Postdoctoral and research appointments:
- National Institute of Haematology and Blood Transfusion, Dept. Cell Metabolism, Budapest, 1972 - present;
- The University of Chicago, Dept. Physiology, Research Associate, 1976-77;
- The Hospital for Sick Children, Dept. Cell Biology, Visiting Associate Professor, 1982-1983;
- The University of North Carolina at Chapel Hill, Visiting Professor, 1990-91; Fulbright Visiting Professor, 2000-2001.
- Hungarian Academy of Sciences, Head of Membrane Biology Research Group, 1996-

Teaching activities:
- 2nd Institute of Biochemistry, Semmelweis Medical University, (courses for graduate students), 1978-81;
- Postgraduate courses in haematology and immunology, 1972 - present;
- Institute of Physiology, Semmelweis Medical University, appointment in teaching general physiology, 1985-1992;
- Full professor habilitation at Semmelweis Medical University, 1995 (biology);
- Ph. D. programs in membrane biochemistry and immunology, Semmelweis Medical University and Eotvos Lorand University, from 1994.

Memberships:
- International Society of Haematology;
American Society of Biochemistry and Molecular Biology
- New York Academy of Sciences;
- American Physiological Society (corresponding member);
- International Cell Research Organization (UNESCO - ICRO panel convenor);
- Hungarian Society of Biochemistry (vice-president);
- Hungarian Biophysical Society;
- FEBS Advanced Course Committee member, 1999-2001;

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Editorial experience:
- Haematologia, managing editor, 1978-82;
- Editor of "Genetics, Structure and Function of Blood Cells", 1980;
- Editor of Biochimica Biophysica Acta, Reviews on Biomembranes,
- Reviewer for Biochimica Biophysica Acta, Cell Calcium, J. Membrane Biology, Haematologia.

Organization of Scientific Meetings:
- International Congress of Haematology, Congress Secretary (1982);
- 20th FEBS Meeting, Secretary of Scientific Program Committee (1990);
- FEBS/ICRO Advanced Courses on "Biochemistry of Membrane Transport", 1989, 1993, 1995, 1998,
- President of the Scientific Committee, FEBS-IUBMB Congress, Budapest, 2005.

Awards:
- Research Awards of the Hungarian Academy of Sciences, 1982, 1986;
- Howard Hughes International Fellowship, 1995-1999; 2000-2004;
- Bela Tanko Award (Hung. Biochem. Soc.), 1995;
- Szechenyi Research Professorship, Hungary, 1997;
- Fulbright Senior Research Fellowship, 2000;
- Research Award of the Hungarian Academy of Sciences, 2003.

Symposium or plenary lectures at International Meetings:
- Conference on "Transport ATPases", New York Acad. Sci, New York, 1982;
- Conference on "Structure and Function of Erythrocytes" Berlin, 1986;
- Symposium on the "Regulation of Cell Volume", 2nd European Congress of Cell Biology, Budapest, 1986;
- Symposium on "Membrane Transport Enzymes", FEBS Meeting, Ljubljana, 1987;
- Symposium on "Calcium Ions and Phosphoinositides", 14th Congress of the IUB, Prague, 1988;
- ICRO Symposium on "Signals and Signal Transduction in the Immune System", Eger (Hungary), 1989;
- Symposium on "Calcium Transport and Calcium Signaling", th FEBS Meeting, Budapest, Hungary, 1990;
- Semmelweis International Symposium on "Calcium transport and calcium pools in human platelets", Budapest, Hungary, 1992;
- Symposium and Advanced Course on "ATP-binding Cassette Transporters", Gosau, Austria, 1997;
- 25th FEBS Meeting, Symposium on Transport ATPases, Copenhagen, Denmark, 1998;
- 26th FEBS Meeting, Symposium on ABC Transporters, Nice, France, 1999;
- Plenary lectures, International Union of Biochemistry and Molecular Biology (IUBMB) Meeting, Birmingham, UK, 2000;
- Symposium and Advanced Course on "ATP-binding Cassette Transporters", Gosau, Austria, 2003;

Publications: see separate list
(over 110 full papers, with a total citation number of about 4,500).

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Balazs Sarkadi - LIST OF PUBLICATIONS

Reviews and book chapters:

1. Gárdos, G., Szász, I. Sarkadi, B.:
Mechanism of Ca-dependent K transport in human red cells.
In: Biomembranes: Structure and Function, (eds. G. Gárdos, I. Szász), Akadémiai Kiadó, Budapest. North Holland P.Co. Amsterdam, pp. 167-180, (1975)

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3. Sarkadi, B., Enyedi, A., Szász, I., Gárdos, G.:
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Patents:

Compounds for Reversing Drug Resistance,
(Sarkadi, B., Seprődi, J., Csuka, O., Magócsi, M., Mező, I., Pályi, I., Teplán, I., Vadász, Zs., Vincze, B.);
Hungarian patent 215 132 (08/11/1998 - appl. number: P 92 03674; filed November 24, 1992); PCT/IB94/00144, application filed on May 12, 1994, WO 95/31474.

2. Assay for Multidrug Resistance
(Sarkadi, B., Homolya, L., Holló, Zs.)
US Patent Number: 5,872,014, Date of Patent: February 16, 1999.

3. Assay and Reagent Kit for the Quantitative In Vitro Determination in Biological Specimens of the Activity of Proteins Causing Multidrug Resistance in Tumors.
(Sarkadi, B., Homolya, L., Holló, Zs.)
Hungarian patent (appl. number: P 94 02551, August 31, 1994; PCT/ HU95/00042, August 31, 1995); PCT: WO 96/06945, International publication date: March 7, 1996; European Patent: EP 0 784 699 B1 (23/07/1997).

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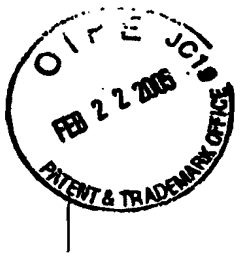

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1632

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	**1340-1-021CIP2 (SJ-0015)**
Inventors:	**Sorrentino and Schuetz**
Serial No.:	**09/866,866**
Filing Date:	**May 29, 2001**
Examiner:	**Li, Qian Janice**
Customer No.:	**31949**
Group Art Unit:	**1632**
Confirmation No.:	**4688**
Title:	**Method of Identifying and/or Isolating Stem Cells and Prognosing Responsiveness to Leukemia Treatment**

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Date of Deposit February 22, 2005

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By _____
Typed Name: Jane Massey Licata, Reg. No. 32,257

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

SUPPLEMENTAL DECLARATION

1. I, Dr. Balazs Sarkadi, M.D., Ph.D., submit this declaration to supplement my Declaration dated October 27, 2003, wherein I identified myself as an expert in the field of ABC transporters, especially as it pertains to the generation of antibodies to ABC transport proteins including BCRP, as evidenced by my curriculum vitae and list of publications.

2. I have reviewed the Office Action issued in this case dated October 21, 2004. I have further reviewed and understand the prior art methods taught by Ross (U.S. Patent No. 6,313,277) and Mechetner et al. (U.S. Patent No. 5,994,088) as identified by the Examiner in the Office Action.

3. As stated in my previous Declaration, I maintain that at as of the priority date of May 31, 2000 there was no *reliable* method known in the art for producing an isolated antibody that recognizes an extracellular portion of the ABC transporter BCRP in a living cell. The production of antibodies to any ABC transporter can only be evaluated on a case-by-case basis as these proteins, while falling within the superfamily of ABC transporters, have individually distinct topologies, post-translational modifications, and protein-protein interactions which may affect their antigenicity.

4. One of skill in the art of antibody production would have appreciated at the time of filing of present application that, while it would be reasonable to try the various methods known in the art, the reasonable expectation of successfully producing an antibody that recognizes the extracellular portion of BCRP in its natural conformation could not be anticipated.

5. As stated in my previous Declaration, Ross suggests an antibody prepared against a purified BCRP protein. Such a purified protein would not be expected to adopt the three-dimensional structure of BCRP as it is found in the cell membrane where it is a half-transporter that forms a fully functional homodimer. As antibodies can recognize conformational epitopes, the three-dimensional structure is critical for production and recognition of an epitope composed of a specific domain (*e.g.*, extracellular portion) in a particular conformation (*e.g.*, the natural conformation).

6. While the Mechetner et al. reference describes a cell-based method for producing an antibody to an ABC transporter, this single success does not change my view on the need to assess any particular method for producing an antibody to an ABC transporter on a case-by-case basis. Only when an antibody is actually produced to a particular ABC transporter can the method used be validated for the production of an antibody to that particular ABC transporter, in particular when a specific domain (*e.g.*, extracellular portion) and conformation (*e.g.*, the natural conformation) is desired.

7. In my recent publication (Ozvegy-Laczka, et al. (Dec. 2004) *J. Biol. Chem.*, submitted herewith), I have used an antibody produced in accordance with the method of U.S. Patent Application Serial No. 09/866,866, (*i.e.*, 5D3) and shown that the interaction of 5D3 with BCRP in intact cells is dependent upon the actual conformation within the transport cycle of this multidrug resistance protein. In contrast, an antibody generated against an N-terminal intracellular epitope of BCRP (*i.e.*, BXP-21) cannot recognize BCRP in a living cell. Therefore, this method is essential to producing an antibody which recognizes an extracellular portion of BCRP in its natural conformation.

I hereby declare that all statements herein of our own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or by imprisonment, or both under §1001 of Title 18 or the United States Code, and that such willful statements may jeopardize the validity of the application, any patent issuing there upon, or any patent to which this verified statement is directed.

Dr. Balazs Sarkadi, M.D. Ph.D.

Date: 01.17.2005.

APPENDIX C – RELATED PROCEEDINGS

None.